Journal of Surgical Oncology 1999;72:77–82

Comparison Between a 2- and 3-Grade System in Predicting Metastatic-Free Survival in Extremity Soft-Tissue Sarcoma

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Background and Objectives: The purpose of this study was to determine whether a histologic grading system consisting of 2 or 3 categories had better discrimination for predicting metastasis-free survival in extremity soft-tissue sarcoma.

Methods: One hundred thirty patients with nonmetastatic soft-tissue sarcoma were identified and the histologic grade (3-grade system) for each tumor was determined. For the 2-grade system, grade was determined by collapsing 3 grades into 2. The Kaplan-Meier method was used to estimate disease free survival.

Results: By use of a 3-grade system, grade 2 tumors showed a 5.2-fold and grade 3 tumors a 9-fold increased risk of systemic relapse when compared with grade 1 tumors. When grade 2 and 3 tumors were combined, they had a 2.6-fold increased risk of systemic relapse compared with grade 1 tumors. When grade 1 and 2 tumors were combined, grade 3 tumors had an 8.4-fold risk of relapse. After data were controlled for size and depth of tumor, each increase in grade in the 3-grade system showed a successive 2.3-fold increase in risk of systemic relapse.

Conclusions: A 3-grade system may be more appropriate for predicting systemic relapse than 2 grades. A prospective study is required to confirm this.

J. Surg. Oncol. 1999;72:77–82.

KEY WORDS: sarcoma; soft-tissue neoplasms; histologic grading

INTRODUCTION

Soft-tissue sarcomas (STS) are a heterogeneous group of tumors with the potential to recur locally after resection and/or to metastasize [1]. There have been numerous studies attempting to identify prognostic factors for STS of the extremities [2–16]. A number of factors, including tumor type, tumor grade, extent of tumor necrosis, number of mitoses, presence of vascular invasion, tumor size, and tumor location (deep to fascia), have been shown to be predictive of systemic relapse either individually or in combination. However, of these factors, tumor grade is the one feature that appears most consistently as being prognostic and has been suggested by some to be the most important criterion [10,15].

Currently no one grading system for STS is uniformly accepted by all pathologists [17,18] although the 2 most common systems used are those of the National Cancer Institute and the French Federation of Cancer Centers (FNCLCC) [2,15,18,19]. Two-, 3-, and 4-grade systems have been used to grade sarcomas. A 2-grade system

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Accepted 20 July 1999

consists of low and high grades [16,20] and may not account for tumors with an intermediate histologic appearance that may have a different prognosis. Although 4-grade systems have been shown to be prognostic [21,22], it is not clear whether the additional grade(s) adds any further discriminatory power in terms of delineating individuals with worse prognosis [17]. The purpose of this retrospective study was to describe a new grading system and to use it to determine whether a 2- or 3-stage system was a better predictor of systemic relapse in patients presenting with nonrecurrent (either local or systemic) STS of the extremity.

MATERIALS AND METHODS

The prospective database at the University Musculoskeletal Oncology Unit, Mount Sinai Hospital, Toronto, was used to identify all patients treated for STS of the extremity by a single surgeon from 1989 to 1994. The upper extremity was defined as the medial border of the scapula to the tips of the fingers, and the lower extremity was defined as extending from the posterior iliac crest to the tips of the toes. Patients were eligible for the study if they received definitive treatment (surgery with or without irradiation) for a nonmetastatic STS of the extremity. As the relationship of local recurrence to systemic disease is controversial, patients who presented to our center with a local recurrence or developed a local recurrence of their tumor, prior to systemic relapse, were excluded. Patients who developed STS in a previous radiation field were also excluded from the study. Any patients who received chemotherapy and/or had a diagnosis of rhabdomyosarcoma, Ewing's sarcoma, or peripheral neuroectodermal tumor were excluded from the study, as these tumors are treated with chemotherapy. Tumors classified as fibromatosis (desmoid), dermatofibrosarcoma protuberans (DFSP), Kaposi's sarcoma, angiosarcoma, or malignant hemangiopericytoma were also excluded from the study. Fibromatosis only recurs locally and pure DFSP is considered a low-grade tumor with no or minimal potential for metastasis. The other tumor types are not commonly graded, as the histologic features do not always correlate with biologic behavior.

One hundred thirty-four eligible patients were identified from a prospective database between February 1989 and December 1994. Four of the eligible cases with margin-positive surgery prior to referral to our center were excluded as tumor tissue was not available for review for this study from the initial resection specimen and the re-excision specimen did not permit grading. In total, 130 patients were included in the study.

The patients were all staged using magnetic resonance imaging or, rarely, computed tomography (CT) of the tumor, diagnostic biopsy, and chest CT. Each case was discussed at a multidisciplinary tumor board conference [23]. External beam irradiation was administered if the surgeon was unable to achieve either a 2-cm normal tissue margin or a fascial margin around the tumor at surgery. Routine follow-up, consisting of a complete physical examination including the local tumor site and chest radiographs, was conducted at 3-month intervals following surgery for 3 years. In years 4 and 5, follow-up was at 6-month intervals and yearly thereafter.

Sarcoma Diagnosis and Grading

Tumor typing was done according to the classification of Enzinger and Weiss [1]. The histologic grade was determined using a modification of a grading system described by Costa et al. [2]. This was done by assessing mitotic activity (>6 mitoses/10 high-power fields, 400× magnification), cellular pleomorphism (present or absent), tumor cellularity (>50% cells to matrix), and tumor necrosis (>15% of the tumor microscopically). Tumors with one feature were considered grade 1; tumors with two features were considered grade 2; and tumors with three or more features were considered grade 3. In addition, certain histiotypes affected grading. Sclerosing or lipoma-like liposarcoma was considered grade 1, myxoid liposarcoma was considered grade 2 unless it had a round cell component of $\geq$5%, and then it was classified as grade 3 [24], and pleomorphic and dedifferentiated liposarcomas were considered grade 3. Sarcomas that could not be typed (sarcoma, not otherwise specified) were considered grade 3 tumors. All tumors were reviewed without knowledge of the clinical course.

To maintain consistency in grading between the 2- and 3-category systems, the 2-grade system was generated by collapsing the 3-stage system. As we did not know whether grade 2 tumors should be considered low or high grade, the 2-grade system was generated in two ways and metastasis-free survival determined for each categorization. For one analysis, grade 1 tumors consisted of a combination of the original grade 1 and 2 tumors (from the 3-stage system) and grade 2 tumors were the original grade 3 tumors (from the 3-stage system). For the second analysis, grade 1 tumors consisted of the original grade 1 tumors only (from the 3-stage system), and grade 2 tumors consisted of a combination of the original grade 2 and 3 tumors (from the 3-stage system).

Data Analysis and Statistics

Data abstracted for this study from the prospective database included patient demographics and tumor descriptors such as site, size, depth, and time to systemic relapse from definitive surgery. Demographic and descriptive variables were analyzed using means, SDs, and frequencies as appropriate. As this was a study of an exploratory nature, grade was defined using multiple categorization as described above for the analysis.

Grade by the number of systemic relapses for each grading system was evaluated using the X^2 test [25]. The

TABLE I. Clinical Characteristics of 130 Patients With Soft-Tissue Sarcoma

Age	55.4 ± 18.8 years (mean ± SD), n = 130
Gender	Male = 63 (48.5%), female = 67 (51.5%)
Site	Shoulder and upper arm = 22 (16.9%)
	Elbow = 14 (10.8%)
	Distal forearm/hand = 8 (6.2%)
	Pelvis/hip = 33 (25.4%)
	Knee = 44 (33.8%)
	Distal leg/foot = 9 (6.9%)
Histologic type	Malignant fibrous histiocytoma = 46 (35.4%)
	Liposarcoma = 43 (33.1%)
	Leiomyosarcoma = 11 (8.5%)
	Synovial sarcoma = 9 (6.9%)
	Sarcoma NOS[a] = 5 (3.8%)
	Others = 16 (12.3%)
Tumor size	7.4 ± 5.5 cm (mean ± SD), range = 1–35 cm
	<5 cm = 72 (55.4%), ≥5 cm = 58 (44.6%)
Depth	Superficial = 29 (22.3%), deep = 101 (77.7%)
Radiation	No = 27 (20.8%), yes = 103 (79.2%)

[a]NOS, not otherwise specified.

method of Kaplan-Meier [26] with censoring was used to evaluate the time to systemic relapse for each grading system using the date of definitive surgery as time zero. After testing for the assumption of proportional hazards, the Cox proportional hazard model [27], controlling for tumor size and depth, was used to evaluate the grading systems. Size and depth were classified according to the American Joint Commission on Cancer definitions, with size dichotomized at 5 cm and depth classified as superficial or deep to fascia [28].

RESULTS

The ages of the 130 patients included in this study ranged from 15 to 88 years (mean, 55.4 ± 18.8 SD). There were 63 male and 67 female patients. Table I provides the clinical details of the sample population. The distribution of the tumor sites was typical of the extremity STS population, with proximal tumors more common than distal. Malignant fibrous histiocytoma, liposarcoma, and leiomyosarcoma were the most common tumor types. Fifty-eight tumors (44.6%) were >5 cm in maximum diameter, and 101 (77.7%) of the tumors were deep to fascia. One hundred three of the patients (79.2%) were treated with surgery and irradiation. All patients with the exception of those who relapsed and died had a minimum follow-up of 2 years. Mean follow-up for the group was 49 ± 26.7 months (mean ± SD), and the median length of follow-up was 55 months (range, 2–108 months). Of 130 patients, 36 (27.7%) had developed systemic disease by 15.0 ± 17.0 months (mean ± SD) and a median of 7.0 months. At last follow-up, 93 patients were alive with no evidence of disease, 9 patients were alive with disease, 21 patients had died because of their sarcomas, and 7 patients had died of other diseases.

Table II shows the frequency distribution for the grading system in relation to the number of systemic relapses and demonstrates the discriminatory ability of the grading criteria. The X^2 statistic for the 3-stage categorizations was statistically significant (P = 0.03), demonstrating increased systemic relapse with increasing tumor grade (Table II). Figures 1 and 2 show the survival curves generated using the Kaplan-Meier method [26] for the 3-stage (Fig. 1) and 2-grade systems. Figure 2A shows the relapse rate for a 2-grade system when grade 1 and 2 tumors were combined and considered grade 1 and the grade 2 tumors were the original grade 3 in the 3-category system. Figure 2B shows the relapse rate for a 2-grade system when grade 1 tumors were the original grade 1 in the 3-category system and grade 2 and 3 tumors were combined together and considered grade 2. The data of Table II and the survival curves suggest that significant prognostic information is lost in a 2-grade system.

TABLE II. Risk of Systemic Relapse by Tumor Grade for Soft-Tissue Sarcoma of the Extremities

	Systemic relapses		Total no. of patients	%
Grading system	No	Yes	(n = 130)	relapses
Grade 1[a]	18	1	19	5.3
2[b]	76	35	111	31.5
Grade 1[c]	45	10	55	18.2
2[d]	49	26	75	34.7
Grade 1	18	1	19	5.3
2	27	9	36	25.0
3	49	26	75	34.7

[a]grade 1 tumors in the 3-category system.
[b]generated by collapse of grades 2 and 3 of the 3-category system.
[c]generated by collapse of grades 1 and 2 of 3-category system.
[d]grade 3 tumors in the 3-category system.

In the 2-grade system, when grades 2 and 3 tumors are combined they have a 2.6-fold increased risk of systemic relapse compared with grade 1 tumors. When grade 1 and 2 tumors are combined, grade 3 tumors have an 8.4-fold risk of relapse. In the 3-stage system, grade 2 tumors had a 5.2-fold increase in risk and grade 3 tumors had a 9-fold increase in risk. Using the method of Cox [27] and after controlling for size (<5 or ≥5 cm) and depth (superficial vs. deep to fascia), there was a 2.3-fold increase in relapse for each successive increase in grade using the 3-stage system (Table III).

DISCUSSION

Tumor grade is an important parameter in predicting prognosis for patients with STS. At present, there is no agreement whether a 2- or 3-category division in histologic grading will better stratify patients as to their risk of systemic recurrence. In this study we attempted to address this question using a single set of criteria for determining grade. The results suggest that a 3-grade sys-

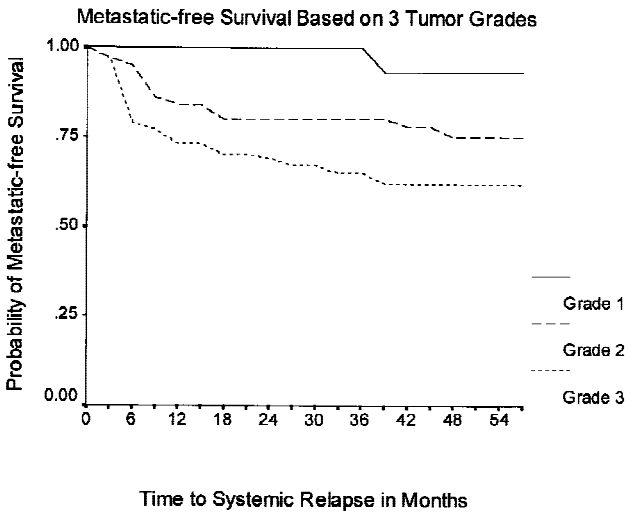

Fig. 1. Kaplan-Meier survival curves according to grade for soft-tissue sarcomas of the extremities.

tem had better discrimination for predicting metastasis-free survival than a 2-grade system. Leyvraz and Costa [29] in a review paper and Enneking [30] in a book chapter both suggested that a 2-grade system may not provide sufficient discriminatory power, and our findings support this. The STS analyzed in this study were all located in extremities, so the findings may not be applicable to sarcomas in other sites, such as retroperitoneum or chest wall. Systemic relapse and not local recurrence was the end point of this study because the factors that predict local relapse, such as positive margins at tumor resection, are different from those for systemic relapse [16], and histologic grade may not be predictive for local control [31].

The importance of separating out grade 1 tumors was demonstrated by the low incidence of relapse in this group. However, it is possible that this low rate may reflect random variation as a result of the smaller sample size compared with grade 2 and 3 tumors and/or the limited follow-up.

Although the grading methods used in this study may have influenced the results, we consider this unlikely for several reasons. First, the histologic features assessed to determine grade in this study included differentiation (or cellular pleomorphism), necrosis, and mitotic activity. These individually or in combination have been used by others as grading criteria and have been shown to be prognostic [2–13]. Second, the statistical analysis indicated that the 3-stage system differentiated increased risk for systemic relapse with grade, suggesting that it was a valid way to grade STS. However, the grading system must still be validated by a prospective study. Third, our findings are similar to those of other grading systems that determined the relative risk of developing metastatic disease in relation to grade. Although it is difficult to compare results directly between studies because not all of the details of the methods of analyses were always provided or different analyses were done, these studies demonstrated risks for systemic relapse ranging from 3.07 to 4.76 [7,8,14–16]. In the two studies using two grades, the risks were 4.3 [16] and 4.76 [8], which were lower than the 8.4-fold increase we observed in this study when grade 2 and 3 tumors were combined for the 2-category system.

It is possible that the method of generating the 2-category system might have affected the results. This approach of collapsing categories was used as there is no consensus as to which of the histologic features used in grading are more important prognostically, and by collapsing categories this allowed for equal weighting of the parameters assessed. Furthermore, the 2-grade system was determined in two ways (grade 2 tumors were combined with either grade 1 or 3 tumors) and each analyzed separately to minimize any potential bias introduced by selection of the tumor groupings. There are two other factors that may have also influenced the findings. This study was retrospective, which may introduce some bias. Also, there is evidence to suggest that tumor histiotype can influence prognosis [7,16], and in a study of 1,041 patients with STS, a diagnosis of leiomyosarcoma was shown to be an independent adverse prognostic factor [16]. It may be that if this sarcoma type had been eliminated from the current study or if they had been considered grade 3 tumors, the findings might have been different.

Although this study suggests that a 3-stage system provides more prognostic information than a 2-grade system, it is unlikely that histologic grading on its own will be sufficient and other features may have to be incorporated into the scheme to be able to separate out all individuals at risk for developing metastatic disease. Coindre et al. [15], using the FNCLCC grading method, demonstrated that grade 3 tumors appeared to be independently prognostic but that this risk decreased with time, suggesting that the length of follow-up may have to be considered. Two studies, one consisting of 354 patients [13] and the other of 546 patients [15], evaluated prognostic features for STS that included both histologic and clinical features; although different criteria were used, both showed a similar metastasis-free rate. Neither of these was completely predictive, as some individuals with low-grade tumors developed systemic relapse. It may be that other tumor characteristics such as the presence of p53 mutations, other molecular abnormalities, and/or a high proliferative index may also influence systemic relapse [32–36].

Given the importance of grading STS, there is a need to develop a grading system that is reliable and reproducible and identifies patients at high risk for developing metastatic disease. On the basis of the results of this

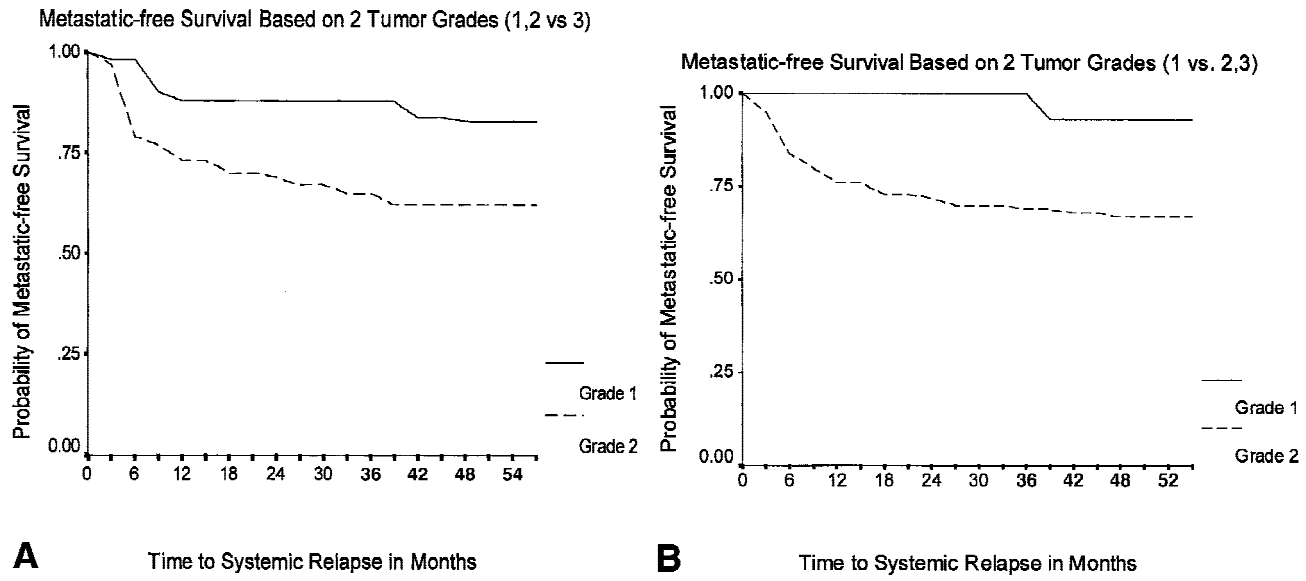

Fig. 2. Kaplan-Meier survival curves for the 2-grade system generated from a 3-stage system for soft-tissue sarcomas of the extremities. **(A)** 1 = grades 1 and 2 and 2 = grade 3 of the 3-grade system. **(B)** 1 = grade 1 and 2 = grades 2 and 3 of the 3-grade system.

TABLE III. Cox Proportional Hazard Model Using the 3-Grade System for Soft-Tissue Sarcoma of the Extremities

Sarcoma characteristics	Risk ratio	95% confidence interval
Size[a]	0.67	0.33–1.35
Depth[b]	2.05	0.70–6.04
Grade	2.30	1.27–4.12

[a]Size dichotomized at <5 and ≥5 cm [27].
[b]Depth was deep to fascia.

study, a 3-stage scheme appears to be more discriminatory than a 2-grade system, but a prospective study is required to confirm these results.

ACKNOWLEDGMENTS

We thank Lori Cutler for her excellent secretarial assistance.

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